

Upon entry of the foregoing amendment, claims 22-33, 35-51, 53, 55-70, 72, 75-81, 84-89, 92-105, 108-114, 118, 120-124, 126-141, 144-152, 156, 158-161, 165-173, 176-195 and 198-219 are pending in the application, with claims 22, 48, 68, 85, 102, 120, 139, 157, 178, 194, 195 and 209 being the independent claims. Claims 32, 46, 66, 137, 160-161, 176, 192, 195 and 207 have been amended to correct formal matters and to more clearly and distinctly define the claimed invention. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Claims 22-31, 35-38, 40-45, 47-51, 53, 55-58, 60-65, 67-70, 72, 75, 76, 78-81, 84-89, 91-93, 95-105, 108, 109, 111-114, 118, 120-124, 126-129, 131-136, 138-141, 144-147, 149-152, 156, 158-161, 165-168, 170-173, 177-191, 193, 207, 209-213 and 215-219 have been allowed.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejoinder of Claims 46, 66, 137, 176, 192 and 207

Applicants thank the Examiner for indicating that claims 46, 66, 137, 176, 192 and 207 have been rejoined and examined.

Claim 207

Applicants note that the Examiner has indicated that claim 207 is allowed in page 2 of the Office Action Summary and has also rejected claim 207 in Paper No. 25, page 3. Applicants believe the Examiner's *indication* of allowance of claim 207 to be in error.

Claim Objections

The Examiner has objected to claims 160-161 because of a typographical error. (Paper No. 25, page 3.) Applicants thank the Examiner for directing Applicants' attention to this error. Claims 160-161 have been amended such that the polypeptide "binds" and antibody. The amendment corrects

the grammatical error objected to by the Examiner. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 32, 33, 39, 46, 59, 66, 77, 94, 110, 130, 137, 148, 169, 176, 192, 194, 195, 198-208 and 214 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Paper No. 25, page 3.)

Specifically, the Examiner has rejected claims 39, 59, 77, 94, 110, 130, 148, 169, 202 and 214 as allegedly being indefinite because the claims are drawn to a method of producing a vector and the starting material of the claims is a vector. The Examiner contends that the "method is then circular and one does not produce anything." (Paper No. 25, page 3.) Applicants respectfully disagree.

The term "vector" as used in the art (i.e. molecular biology) refers to a carrier/deliverer of nucleic acids, both in the case where the vector actually is associated with a nucleic acid insert and in the case where the vector is not associated with a nucleic acid insert. *Compare* Invitrogen, 2001 Catalog, p.73 (Exhibit A) (term "vector" used to describe an expression tool that is not associated with a DNA insert) *with* Hodgson, C.P., *Bio/Technology* 13: 222-25 (1995) (Exhibit B) (term "vector" used to describe an expression tool that is associated with a DNA insert); *see also* U.S. Pat. No. 6,143,498 (Exhibit C) (claim 8); U.S. Pat. No. 6,130,079 (Exhibit D) (claim 9); U.S. Pat. No. 5,998,171 (Exhibit E) (claim 12). In the instant case, the vector produced by the method of the claims would be different than the vector used as the starting material because the vector produced would comprise an isolated polynucleotide of the claims. Thus, the "starting material" of the method and the product of the method are different. This distinction would be immediately apparent to one of ordinary skill in the art.

The purpose of the requirement for definiteness is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent and

to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. § 112, first paragraph. (M.P.E.P. § 2173.) Applicants assert that the instant claims meet this purpose. It would be plain to one of ordinary skill in the art that the vector produced by the method of the claims is distinct from the vector used as the starting material. Thus, Applicants submit that the claims are not indefinite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 46, 66, 137, 176, 192 and 207 as allegedly being indefinite because there is insufficient antecedent basis for the limitation "said ligand" in the claims. Applicants have amended claims 46, 66, 137, 176, 192 and 207 so that antecedent basis for the limitation "said ligand" is established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claim 32 as allegedly being indefinite because there is insufficient antecedent basis for the limitation "said reference nucleic acid" in the claim. Claim 32 is dependent to claim 29, which is dependent to claim 26, which is further dependent to independent claim 22. Applicants have amended claim 32 so that it recites "said second nucleic acid" instead of "said reference nucleic acid." Antecedent basis for "said second nucleic acid" can be found in claim 22. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claim 176 as allegedly being indefinite because it depends on a canceled claim. Applicants have amended claim 176 such that it is no longer dependent on a canceled claim. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has alleged that claims 194 and 195 are confusing. The Examiner appears to be of the opinion that claim 195, which depends from claim 194, does not further limit claim 194. Specifically, the Examiner has stated:

Claim 194 is unclear because it cannot be determined in light of claim 195 if the hybridization must occur under the stated conditions to a

nucleic acid consisting of nucleotides complementary to 88-732. If claim 194, which claim 195 depends on, must hybridize to the complement of nucleotides 88-732 of SEQ ID NO:1, wouldn't said nucleic acid of claim 194 also necessarily hybridize under the recited conditions to the complement of nucleotides 412 to 681? If yes, then claim 195 is not further limiting. If no, then the polynucleotide of claim 195 would not be enabled as it must encode a polypeptide which binds TRAIL.

(Paper No. 25, page 4.) (Citation omitted)

While not acquiescing to the Examiner's rejection, Applicants have amended claim 195 in order to advance prosecution. Claim 195 has been rewritten in independent form and the functional limitation has been deleted from the claim. Thus, the Examiner's concerns have been obviated. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 195 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claim. The Examiner asserts that "the specification, while being enabling for a polynucleotide that hybridizes to the complement of nucleotides 412-681 of SEQ ID NO:1 and is not limited by a function, or for the polynucleotide of claim 194 (i.e. hybridizes to complement of 88-732 of SEQ ID NO: 1), does not reasonably provide enablement for a polynucleotide that hybridizes to the complement of nucleotides 412-681 of SEQ ID NO:1 *and* is required to bind TRAIL" (Paper No. 25, page 4.) (Emphasis in original.) Specifically, the Examiner has stated that "[i]t is not disclosed what portion of the ECD is responsible for ligand binding" and that the nucleic acid of the claim "does not need to encode the full ECD." (Paper No. 25, page 5.) Thus, the Examiner has concluded that "[i]t is unpredictable how similar and how long the encoded polypeptide needs to be compared to ECD of SEQ ID NO:2 to bind TRAIL" and that "[i]t would require undue experimentation to make the invention commensurate in scope with the claim." (*Id.*) Applicants respectfully disagree.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Some experimentation is permitted so long as the experimentation necessary to practice the invention is not undue. *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).

As noted in Applicants' Amendment and Reply of August 31, 2000, the specification teaches at page 1, line 21 through page 4, line 2, and in the references cited therein, that a great deal is known about the ligand-binding domains of the TNF-family receptors. For example, it is well known that specific conserved cysteine residues must be present for ligand binding to take place (e.g. amino acid 132 of SEQ ID NO: 2). The specification also teaches polypeptides with deletions of N-terminal amino acids up to the cysteine at position 132 and deletions of C-terminal amino acids up to the cysteine at position 221 of SEQ ID NO: 2 may "retain some biological activity such [as] receptor binding." (Specification, page 22, lines 1-35.) Thus, contrary to the Examiner's suggestion, the portion of ECD important for ligand binding is disclosed. Further, Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including DR4, which illustrates the conserved amino acids in the ligand binding extracellular domain important for TNF-family ligand binding activity. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the ligand binding domains of the several TNF-family receptors and thereby reasonably predict which conserved amino acids located between amino acids 131 and 222 of SEQ ID NO: 2 are required for ligand binding.

Further, at the time of filing, the TNF-family ligand TRAIL had been reported in the literature. (See Specification at page 3, line 22 to page 4, line 15, and the cited references therein.) Accordingly the TRAIL ligand was readily available for use in ligand binding assays. The specification further teaches hybridization conditions (page 11, line 22 to page 12, line 9), methods to screen for ligand binding (page 31, line 3 to page 32, line 28), conservative amino acid substitutions (page 23, line 37 through page 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions

(page 25, lines 4-13). Given the high level of skill in the art regarding the structure of TNF-family receptor ligand binding domains, the teachings in the specification as to which amino acids must be conserved, methods to make conservative substitutions, how to test for TRAIL binding, and hybridization conditions to be utilized in hybridization studies, it would require only simple and routine experimentation for one of ordinary skill in the art to determine which polynucleotides hybridize to the region of the SEQ ID NO: 2 recited in the claims and encode a polypeptide capable of binding TRAIL. Thus, the quantity of experimentation is not unreasonable or undue.

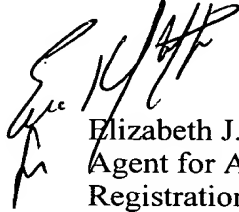
However, solely to advance prosecution and not in acquiescence to the Examiner's rejection, Applicants have rewritten claim 195 in independent form and have removed its functional limitation. As Applicants understand the Examiner's statements, the claims, as amended, are enabled and accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C



Elizabeth J. Haanes, Ph.D.
Agent for Applicants
Registration No. 42,613

Date: 2/16/01

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

P:\Users\PC Choi\1488\130\reply.wpd
SKGF Rev. 1/26/01